REMARKS

Applicants have cancelled claims 2, 3, 4, and 47 without prejudice expressly reserving the right to pursue the subject matter of the cancelled claims in one or more subsequently filed applications.

Applicants have amended claims 1 and 46 such that the subject in need thereof suffers from multiple sclerosis.

Claims 1-4, 6-8, 10-13, 15-16, 18-20, 22-24, 46-48 and 52-56 stand rejected under 35 U.S.C. 112 first paragraph for purportedly lacking enablement.

Although Applicants disagree, Applicants have amended claims 1 and 46 to identify the subject in need thereof as a subject who suffers from multiple sclerosis. The Examiner states that the specification is enabling for a method of promoting remyelination of nerve cells or reversing paralysis in a multiple sclerosis subject. Thus, the currently amended claims are enabled by the specification.

In view of the foregoing remarks and amendments to the claims, Applicants request that the Examiner reconsider and withdraw the rejection of Claims 1-4, 6-8, 10-13, 15-16, 18-20, 22-24, 46-48 and 52-56 stand rejected under 35 U.S.C. 112 first paragraph for purportedly lacking enablement.

Claims 1-4. 6-8, 10-13, 15-16, 18-20, 22-24, 46-48 and 52-56 stand rejected under 35 U.S.C. 102 (a) for purportedly being anticipated by National Horizon Scanning Center article (July 2002)("National Horizon") In view of the following remarks, Applicants request that the Examiner reconsider and withdraw the rejection.

National Horizon administers natalizumab or placebo every 4 weeks for 6 months and states that the subjects had fewer brain lesions and fewer relapses than untreated patients. But National Horizon indicates that the treated patients were still developing new brain lesions and still displayed relapses.

Thus while the National Horizons treatment regimen may have slowed an aspect of disease progression, National Horizon does not teach a method that promoted *remyelination* or *reversal of paralysis*. Therefore, National Horizon does not teach Applicants' method for promoting remyelination of nerve cells by chronically administering an antibody that binds to alpha-4 beta-1 integrin, e.g., natalizumab, in a remyelinating effective amount weekly or monthly over a period of at least 6 months, or at least one year as recited in claims 18 and 56. As such New Horizon does not anticipate the invention as claimed.

Claims 1-4, 6-8, 10-13, 15-16, 18, 46-48 and 52-56 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over Tubridy et al. (Neurology 1999 Aug. 11; 53(3):466-72)("Tubridy"). In view of the following remarks, Applicants request that the Examiner reconsider and withdraw the rejection of the claims.

Applicants submit that their teaching for chronic administration of natalizumab has displayed unexpected benefits in the treatment of demyelinating conditions, e.g., multiple sclerosis. As discussed in Applicants' previous response dated September 29, 2008, Munschauer and Polman submitted with that response, further support Applicants disclosure that the chronic administration of natalizumab over time not only promote remyelination but it also reverses paralysis in subjects.

Promoting remyelination is to promote repair and/or regeneration of the myelin sheath of nerve cells. Promoting remyelination is significantly different from stopping disease progression. Applicants submit that any method used to treat multiple sclerosis that treats and stops disease progression might treat and stop myelin degradation. However, *stopping* disease progression, including the loss of the myelin sheath, is distinct from *promoting repair* and/or *regeneration* of the myelin sheath. The knowledge that certain compounds are useful for treating and stopping myelin degradation would not lead one of ordinary skill in the art to understand that the compounds could be used to promote repair and/or

regeneration of the myelin sheaths. In fact, industry thinking may be to the contrary, Applicants submit that those of skill in the art continue to search for therapies to promote remyelination. According to Dubois-Dalcq et al. (Enhancing Central Nervous System Remyelination in Multiple Sclerosis, Neuron, vol. 48, 9-12, 2005), "[w]hile therapies designed to reduce inflammation can decrease the disease burden, they do not directly address the question of myelin repair in chronic disease. Recent advances in the stem cell field, and in particular the biology of adult neural precursor cells, have raised hopes that remyelinating therapies *may soon be developed...*(emphasis added)" Thus, at the time of this invention, there was a long-felt, but unsolved, need for remyelinating therapies. The cited references do not teach or suggest Applicants' claimed method for promoting remyelination.

In particular, Tubridy administered anti-α4 integrin antibody in two IV infusions 4 weeks apart and then followed the patients for 24 weeks. Tubridy teaches that at 12 weeks the treated group exhibited significantly fewer new active lesions and fewer new enhancing lesions than the placebo group but by 24 weeks there were *no significant difference* in the number of new active or new enhancing lesions between the groups. Thus Tubridy teaches a regimen that may *slow* progression of the disease, but there is no teaching or suggestion of a regimen that stops disease progression or would *promote remyelination or reverse paralysis*.

Tubridy states that their study was not designed to look definitively at the effect of treatment on relapse rate and that the correlation between disability and changes seen on MRI would require a larger longer term trial and that the use of higher doses and chronic administration would require further studies. Based on such a general suggestion for approaching further studies, and based on the knowledge that prior to Applicants' invention none of the available treatments promoted remyelination or reversed paralysis, one of skill in the art would not have had a reasonable expectation that an anti-α4 integrin antibody

would promote remyelination and actually reverse paralysis. Therefore, the remyelination and reversal of paralysis produced by Applicants' claimed method of chronically administering of a remyelinating amount of anti-α4 integrin antibody, e.g., natalizumab, over a period of at least 6 month, or at least year (for claims 18 and 56) is a surprising and unexpected result. As such Tubridy does not render Applicants' invention as claimed obvious and applicants request that the Examiner reconsider and withdraw the rejection of the claims 1-4, 6-8, 10-13, 15-16, 18, 46-48 and 52-56 under 35 U.S.C. 103(a) for purportedly being unpatentable over Tubridy et al.

Claims 1-4, 6-8, 10-13, 15-16, 18, 46-48 and 52-56 stand rejected under 35 U.S.C. § 103(a) for purportedly being unpatentable over U.S. Patent No. 5,840,299 ("the '299 Patent") in view of Tubridy. In view of the following remarks, Applicants request that the Examiner reconsider and withdraw the rejection.

As discussed above, Applicants' teachings for chronic administration of natalizumab has displayed unexpectedly significant benefits in the treatment of multiple sclerosis, i.e., for the first time a treatment has produced *remyelination and reversal of paralysis* in MS patients. Additional reports have published that support Applicants' teachings that the chronic administration of natalizumab over time not only promotes remyelination but it also reverses paralysis in subjects. In addition to Munshauer and Polman submitted with Applicants' previous response, Applicants submit herewith Zivadinov et al. "Natalizumab (Tysabri) Promotes Remyelination in Patients with Multiple Sclerosis. A Voxel-Wise Magnetization Transfer Imaging Case-Control Study" presented April 28, 2009 at the American Academy of Neurology (AAN), which further demonstrates that chronic administration of natalizumab in remyelinating effective amounts resulted in remyelination and stabilizes demyelination.

Applicants submit that the '299 Patent and Tubridy in combination fail to suggest the unexpected benefits produced by Applicants' method as currently claimed.

The '299 Patent does not teach the chronic administration of the antibody over a period of at least 6 months or at least 1 year and is silent regarding "remyelination of nerve cells" and "reversing paralysis." Furthermore, Tubridy teaches that at 24 weeks after patients received two IV administration of anti-α4 integrin antibody 4 weeks apart there were no significant difference in the number of new active or new enhancing lesions between the groups of treated and control patients. Thus Tubridy teaches a regimen that may *slow* progression of the disease, but there is no teaching or suggestion of a regimen that would *promote remyelination or reverse parlysis.* Likewise, National Horizon, teaches that administration of natalizmab every four weeks for six months only slowed the occurrence of new brain lesions but does not teach the surprising and unexpected result that chronic treatment with an antibody such as natalizumab over a period of at least 6 months or at least a year actually promotes remyelination and reversal of paralysis. Thus one of skill in the art considering the '299 Patent in combination with Tubridy would not expect that the chronic administration of natalizumab over a period of at least 6 months, or at least a year for claims 18 and 56, would promote remyelination and reverse paralysis.

Thus, evaluating the '299 Patent and Tubridy in combination and in the context of the state of the art at the time of filing, and considering that prior to Applicants' invention no treatment regimen had produced remyelination or reversal of paralysis, one of skill in the art would not have reasonably expected and would be surprised that the chronic administration of a remyelinating amount of an anti-α4 integrin, e.g., natalizumab, would promote remyelination and reverseof paralysis. Thus the combination of the '299 Patent and Tubridy fail to render the invention as currently claimed obvious and Applicants request

that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 103(a)

Claims 1-4, 19-20 and 22-24 stand rejected under 35 U.S.C. 103(a) for purportedly being unpatentable over the '299 Patent in view of Tubridy and further in view of US Patent No. 6,753,135 "as set forth in the previous Office Action mailed April 11, 2006."

Applicants note that this combination of references are not set forth in the Office Action dated April 11, 2006 and therefore request clarification of this rejection, so that they may respond accordingly.

If there are any questions regarding this amendment or the application in general, a telephone call to the undersigned would be appreciated since this should expedite the prosecution of the application for all concerned.

If necessary to effect a timely response, this paper should be considered as a petition for an Extension of Time sufficient to effect a timely response, and please charge any deficiency in fees or credit any overpayments to Deposit Account No. 05-1323 (Docket #103930.B080061).

Respectfully submitted,

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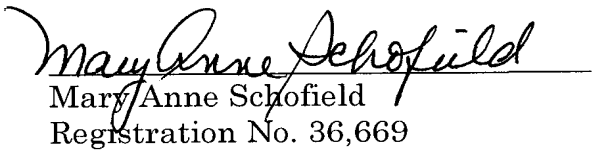

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